JACC Vol. 14, No. 6
November 15, 1989:1464–73

Type 1 Fiber Abnormalities in Skeletal Muscle of Patients With Hypertrophic and Dilated Cardiomyopathy: Evidence of Subclinical Myogenic Myopathy

ALIDA L. P. CAFORIO, MD,* BRUNO ROSSI, MD,† RICCARDO RISALITI, MD,† GABRIELE SICILIANO, MD,† ANTONIO MARCHETTI, MD,‡ CORRADO ANGELINI, MD,§ FILIPPO CREA, MD,‖ MARIO MARIANI, MD,* ALBERTO MURATORIO, MD†

Pisa and Padova, Italy and London, England

Abnormalities of skeletal muscle have been described in patients with dilated and hypertrophic cardiomyopathy. Eleven patients with dilated and eight with hypertrophic cardiomyopathy without overt symptomatic skeletal myopathy underwent extensive neuromuscular studies. Quantitative electromyography showed abnormal reduction of motor unit potential duration, indicative of myogenic myopathy, in four patients (36%) with dilated and in three (37%) with hypertrophic cardiomyopathy. Values were 21% to 40% (mean 28%) lower than those in age-matched normal control subjects. The presence of normal nerve conduction velocities and of normal motor unit fiber density in all patients indicated lack of neurogenic abnormalities.

Skeletal muscle biopsy was performed in five patients with dilated and in four with hypertrophic cardiomyopathy. In all nine patients light and electron microscopy showed central hyporeactive cores, selective atrophy and mitochondrial abnormalities of type 1 fibers but not of type 2 fibers. The degree of impairment of left ventricular function in patients with electromyographic abnormalities was similar to that of those without (percent fractional shortening at two-dimensional echocardiography 21 ± 9 versus 25 ± 10, ejection fraction at angiography 39 ± 13% versus 42 ± 13% and left ventricular end-diastolic pressure 21 ± 6 versus 21 ± 8 mm Hg) as well as symptom duration (9 ± 4 versus 12 ± 8 months).

Thus, subclinical electromyographic alterations indicative of myogenic myopathy are frequent in patients with dilated and hypertrophic cardiomyopathy and are unrelated to the degree of impairment of left ventricular function. The concomitant histologic alterations, characterized by selective type 1 atrophy, are similar to those observed in congenital and idiopathic myopathies, but different from those described in secondary heart failure.

(J Am Coll Cardiol 1989;14:1464–73)

After the first histopathologic study by Shafiq et al. (1), several authors (2–9) showed the existence of a broad spectrum of electromyographic or histologic abnormalities, or both, in skeletal muscle of patients with dilated (2–4) and hypertrophic cardiomyopathy (5–9). However, no consensus exists as to whether these abnormalities are neurogenic (8,9) or myogenic (2–7) in origin. To establish the nature of skeletal muscle abnormalities in patients with primary myocardial disease, 11 patients with dilated and 8 patients with hypertrophic cardiomyopathy were submitted to extensive neuromuscular studies. Assessment of skeletal muscle function was based on standard and computerized quantitative electromyographic studies, light and electron microscopic analysis and determination of mitochondrial oxidative enzyme levels in skeletal muscle biopsy specimens.

Methods

Study patients (Table 1). Thirty patients with primary myocardial disease were admitted to our department from January 1985 to September 1986. Nineteen of them form the basis of this report; the others would not consent to enter this study. Eleven of the 19 patients (8 men, 3 women, mean age 48.6 ± 13.8 years) had dilated cardiomyopathy; 8 pa-

From the *Cattedra di Malattie dell'apparato cardiovascolare, †Istituto di Clinica Neurologica, and ‡Istituto di Anatomia Patologica, University of Pisa, Pisa, Italy, the §Istituto di Clinica Neurologica, University of Padova, Padova, Italy, and ‖the Cardiovascular Research Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London, England.

Manuscript received November 7, 1988; revised manuscript received May 24, 1989, accepted June 2, 1989.

Address for reprints: Alida L. P. Caforio, MD, Cardiological Sciences, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, England.

0735-1097/89/$3.50

Table 1. Clinical, Echocardiographic and Hemodynamic Characteristics of the 19 Study Patients

	Clinical						Echocardiographic			Hemodynamic			
Patient No.	Gender/ Age (yr)	Symptom Duration (mo)	NYHA Class	Palpitation	Effort Chest Pain	Syncope	LVIDd (cm)	%FS	Max WT (cm)	PCWP (mm Hg)	LVEDP (mm Hg)	EF (%)	LV Gradient (mm Hg)
DCM													
1	M/55	12	I	+	–	–	5.9	27	0.7	11	13	45	–
2	M/19	10	I	+	–	–	5.8	23	0.7	12	14	40	–
3	F/30	24	II	+	–	–	6.0	25	0.9	13	14	36	–
4	M/48	7	II	+	–	–	6.5	25	0.8	12	13	40	–
5	M/60	12	II	–	–	–	6.0	27	1.1	15	25	43	–
6	M/55	7	III	–	–	–	6.5	10	1.2	27	22	25	–
7	F/64	6	III	+	–	–	6.7	13	1.1	25	20	27	–
8	M/56	5	III	+	–	–	6.5	15	1.3	25	19	28	–
9	M/53	5	III	+	–	–	6.6	15	0.9	20	21	30	–
10	M/39	7	III	+	–	–	7.4	5	0.8	34	39	20	–
11	F/56	6	III	+	–	–	6.7	10	0.7	28	33	25	–
HCM													
12	M/47	–	I	–	–	–	5.0	36	1.7	5	14	60	–
13	M/47	12	I	–	+	–	5.2	34	1.8	7	15	60	40
14	M/47	24	I	+	+	+	4.8	35	2.2	5	13	52	45
15	M/40	10	I	+	+	–	5.0	37	2.4	10	17	62	35
16	F/27	7	II	–	+	+	4.5	32	2.3	11	30	40	65
17	M/38	24	II	–	+	+	4.7	30	1.9	13	30	50	55
18	M/41	12	II	+	–	–	5.0	27	2.4	14	22	47	84
19	F/48	15	III	+	–	–	5.5	25	2.2	14	20	45	45

DCM = dilated cardiomyopathy; EF = ejection fraction; %FS = % fractional shortening; HCM = hypertrophic cardiomyopathy; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVIDd = left ventricular internal end-diastolic dimension; Max WT = maximal (septal) wall thickness; NYHA = New York Heart Association classification; PCWP = mean pulmonary capillary wedge pressure; – = absent; + = present.

tients (6 men, 2 women, mean age 44.2 ± 13.8 years) had hypertrophic cardiomyopathy (7 obstructive, 1 nonobstructive; all of them had asymmetric septal hypertrophy). Mean body weight was 71 ± 10 kg; all patients were within the range of the ideal weight (10).

At the time of examination, six were in New York Heart Association functional class I, six in class II and seven in class III. Cardiovascular assessment was performed 1 to 3 weeks before entering the study and included M-mode and two-dimensional echocardiography, right and left sided cardiac catheterization, selective coronary arteriography and left ventriculography in two orthogonal projections.

Dilated cardiomyopathy was diagnosed according to the World Health Organization criteria (11,12). Hypertrophic cardiomyopathy was diagnosed according to accepted classifications, in the presence of unexplained left ventricular hypertrophy (13,14). No patient had a history of myocarditis, coronary artery disease, systemic hypertension, peripheral vascular disease, diabetes mellitus or excessive ethanol consumption, or a history or signs of renal failure, hereditary or acquired neuromuscular disorders or associated syndromes; nor had any patient consumed neurotoxic drugs, including those that cause axonal neuropathy (15). Clinical findings are summarized in Table 1. All patients gave written, informed consent as approved by the local Ethics Committee.

Neuromuscular assessment. A detailed clinical history and physical examination were performed. The Medical Research Council grading system (16,17) was applied to quantitate segmental strength in the following muscles: deltoid, biceps and triceps brachii, extensor carpi, quadriceps femoris and foot dorsal flexors. Serum determinations were performed for creatine kinase, myoglobin, lactate in basal conditions and after a 10 min forearm ischemic test (18), and carnitine, both in its free and esterified forms (19).

Electromyographic studies. In all patients qualitative evaluation of skeletal muscle function was obtained by a standard electromyographic test and interference pattern analysis at maximal voluntary contraction in the right biceps brachii muscle (20). Spontaneous activity (fibrillation, positive sharp waves) at the standard test or recruitment with fast firing rate at interference pattern analysis, or both, were considered qualitative indexes of neurogenic damage (21).

Objective assessment of skeletal muscle abnormalities of myogenic origin at quantitative electromyographic analysis was based on the following determinations: 1) single motor unit potential duration (13 patients) in vastus medialis (OTE–Basis S09 program, single motor unit), calculated as the

JACC Vol. 14, No. 6
November 15, 1989:1464–73

mean of 20 values obtained from different sites of the muscle (20); 2) ratio between mean amplitude of turns and mean turn count per s, of an interference pattern in the right biceps brachi muscle (18 patients), according to Willison analysis (22–24); and 3) muscle fiber conduction velocity in the left biceps brachii short head (18 patients), calculated as the mean of values from 20 different fibers (25).

Objective assessment of skeletal muscle abnormalities of neurogenic origin was based on the following determinations: 1) sensory and motor nerve conduction velocities in the upper limb (left ulnar nerve) and lower limb (left sural nerve) in 19 patients (20) and 2) motor unit fiber density in the extensor digitorum communis muscle (13 patients), calculated as mean number of potentials from 20 different positions of the recording electrode (26). Values were considered abnormal when they exceeded 2 SD from the mean control value for our laboratory. Only single motor unit potential duration was compared with Buchthal age-matched control values (27). To assess reproducibility between our measurements and those from Buchthal's laboratory we had previously determined single motor unit potential duration in 10 normal subjects aged 25–35 years, and the values obtained (mean ± SD 11.3 ± 1.1 ms) were similar to age-matched reference values (27).

Muscle biopsy. Nine patients underwent open muscle biopsy. In six it was performed in the right biceps brachii and in three in the right deltoid muscle. The specimens were separated into three parts; two of them were cooled for 10 to 15 s in an isopentane bath immersed in −160°C liquid nitrogen and kept at −80°C for light microscopic and biochemical examination. The third fragment was immersed in 2.5% phosphate-buffered glutaraldehyde for electron microscopy. Light microscopy was performed after staining with hematoxylin-eosin, modified Gomori trichrome, periodic acid-Schiff, oil-red-O, reduced diphosphopyridine nucleotide-tetrazolium reductase and alkaline adenosine triphosphatase (pH 9.4). Electron microscopy was performed as previously described (28,29). Percent distribution of type 1 and 2 fibers, mean diameter, diameter variability coefficient, atrophy and hypertrophy factors in both type 1 and 2 fibers were calculated (28). Mean diameter was considered to be reduced in patients in whom it was lower than the lowest value of the normal range according to Dubowitz and Brooke (28).

Free and esterified carnitine radioimmunoassay and spectrophotometric assay (19) of citrate synthetase, succinic dehydrogenase, reduced diphosphopyridine nucleotide dehydrogenase, succinic-cytochrome C-reductase, reduced diphosphopyridine nucleotide-cytochrome C-reductase and cytochrome C-oxidase were carried out in two patients with dilated and in four with hypertrophic cardiomyopathy. Enzyme activities were considered abnormally reduced when lower than the lowest value of the normal range as reported by Angelini et al. (19).

Table 2. Results of Quantitative Electromyographic Analysis in the 19 Study Patients

Patient No.	Single Motor Unit Potential Duration (ms)*	Muscle Fiber Conduction Velocity (m/s)	Willison Ratio (mV/turns)	Fiber Density
DCM				
1	11.80 (13 ± 1.30) (N)	3.74 (N)	1.99 (N)	1.65 (N)
2	0	3.98 (N)	1.98 (N)	1.17 (N)
3	9.47 (11.1 ± 1.10) (N)	3.84 (N)	1.72 (N)	1.65 (N)
4	10.00 (13.0 ± 1.30) (↓)	0	1.43 (N)	1.30 (N)
5	12.54 (13.7 ± 1.35) (N)	4.82 (N)	1.61 (N)	0
6	10.62 (13.4 ± 1.30) (↓)	4.44 (N)	1.85 (N)	1.40 (N)
7	0	3.29 (N)	1.29 (N)	1.35 (N)
8	0	3.88 (N)	1.47 (N)	0
9	8.26 (13.4 ± 1.30) (↓)	3.59 (N)	1.56 (N)	0
10	0	2.72 (↓)	1.63 (N)	0
11	9.77 (13.4 ± 1.30) (↓)	5.09 (↑)	1.58 (N)	1.45 (N)
HCM				
12	10.15 (12.5 ± 1.25) (N)	3.31 (N)	1.47 (N)	1.35 (N)
13	8.14 (12.5 ± 1.25) (↓)	3.75 (N)	1.59 (N)	1.23 (N)
14	10.70 (12.5 ± 1.25) (N)	3.95 (N)	0	1.30 (N)
15	9.85 (12.2 ± 1.25) (N)	3.02 (↓)	1.75 (N)	0
16	0	3.45 (N)	1.29 (N)	1.30 (N)
17	0	3.58 (N)	1.42 (N)	0
18	9.86 (12.5 ± 1.25) (↓)	4.19 (N)	1.64 (N)	1.46 (N)
19	9.68 (13.0 ± 1.30) (↓)	3.48 (N)	1.30 (N)	1.45 (N)
Normal	*	4.07 ± 0.40 (n = 23)	1.33 ± 0.46 (n = 15)	Age <50: 1.49 ± 0.16 Age >50: 1.57 ± 0.17

*Age- and gender-matched values for single motor unit potential duration (mean ± SD) according to Buchthal (27) are indicated in parentheses. N = normal value; ↓ = reduced value (<mean − 2 SD); ↑ = enhanced value (>mean + 2 SD); 0 = not done; other abbreviations as in Table 1.

Statistical analysis. Ventricular function and symptom duration in patients with and without electromyographic abnormalities were compared by Student *t* test for unpaired data. The mean values of atrophy factors in patients in the different functional classes were compared with use of one-way analysis of variance. Fisher's exact test was used to compare proportions of patients with electromyographic abnormalities belonging to pairs of the different functional classes. Statistical significance was defined as $p < 0.05$. All data are expressed as mean values ± 1 SD.

Results

Neuromuscular clinical findings. Medical history revealed the occurrence of muscular pain in three patients (27%) with dilated cardiomyopathy and in five (62%) with hypertrophic cardiomyopathy. It was mostly described as sporadic, occurring at rest and located in forearms or calves. All symptomatic patients with dilated and one patient with hyper-

Table 3. Morphometric Findings of Muscle Biopsy in 9 Patients

Patient No.	Type 1 Fibers				Type 2 Fibers			
	% Distribution	Mean Diameter (μ)	Diameter Variability Coefficient	Atrophy Factors	% Distribution	Mean Diameter (μ)	Diameter Variabiity Coefficient	Atrophy Factors
DCM								
1	37 (N)	39.8 (↓)	220 (N)	400 (↑)	63 (N)	50.2 (N)	164 (N)	90 (N)
6	60 (↑)	41.0 (N)	238 (N)	680 (↑)	40 (N)	50.7 (N)	189 (N)	120 (N)
8	38 (N)	41.1 (N)	243 (N)	620 (↑)	62 (N)	53.8 (N)	184 (N)	80 (N)
9	41 (N)	37.7 (↓)	249 (N)	800 (↑)	59 (N)	49.6 (N)	147 (N)	40 (N)
11	33 (N)	36.3 (N)	170 (N)	160 (↑)	62 (N)	39.4 (N)	178 (N)	80 (N)
HCM								
12	41 (N)	38.4 (↓)	242 (N)	760 (↑)	59 (N)	66.7 (N)	199 (N)	40 (N)
14	38 (N)	41.7 (N)	134 (N)	400 (↑)	62 (N)	52.9 (N)	128 (N)	25 (N)
16	42 (N)	47.7 (N)	226 (N)	80 (N)	58 (N)	40.2 (N)	176 (N)	80 (N)
18	41 (N)	45.6 (N)	222 (N)	400 (↑)	59 (N)	56.3 (N)	181 (N)	40 (N)
Normal								
Male		40 to 80		≤150		40 to 80		
	≤55%		≤250		≤80%		≤250	≤150
Female		30 to 70		≤100		30 to 70		

*See reference 28. Abbreviations and symbols as in Tables 1 and 2.

trophic cardiomyopathy also showed a slight hyposthenia in girdles or proximal limbs, or both (score 4 on Medical Research Council scale), but not in the distal muscles of upper and lower limbs. All of them were in New York Heart Association functional class III. No patient had muscular hypotrophy. Serum creatine kinase, myoglobin, free carnitine and lactate values after the ischemic test were normal in all patients. Esterified carnitine was reduced in one patient with hypertrophic cardiomyopathy.

Electromyographic studies (Table 2). At standard electromyography, myogenic motor unit potential morphology (reduced amplitude and duration, enhanced polyphasia) was observed in one patient with dilated and in three patients with hypertrophic cardiomyopathy. Quantitative electromyography yielded abnormal results in these four patients and in five other patients (four with dilated and one with hypertrophic cardiomyopathy). The following abnormalities, typical of myogenic myopathy (20,25,27), were found: 1) reduction of single motor unit potential duration in three patients with dilated and three with hypertrophic cardiomyopathy; 2) alteration of muscle fiber conduction velocity in two patients (one with dilated and one with hypertrophic cardiomyopathy); and 3) both reduction of single motor unit potential duration and alteration of muscle fiber conduction velocity in one patient with dilated cardiomyopathy. Willison ratio was within the normal range in all patients. No patient showed signs of neurogenic alteration (spontaneous activity, recruitment with fast firing rate, reduction of nerve motor and sensory conduction velocities) (20,26).

Muscle Biopsy Findings (Table 3)

Light microscopy. Pathologic changes of type 1 fibers were detected in all nine patients from whom a biopsy specimen was obtained (Fig. 1). Type 1 fiber abnormalities included central hyporeactive cores (Fig. 2) or strong sub-

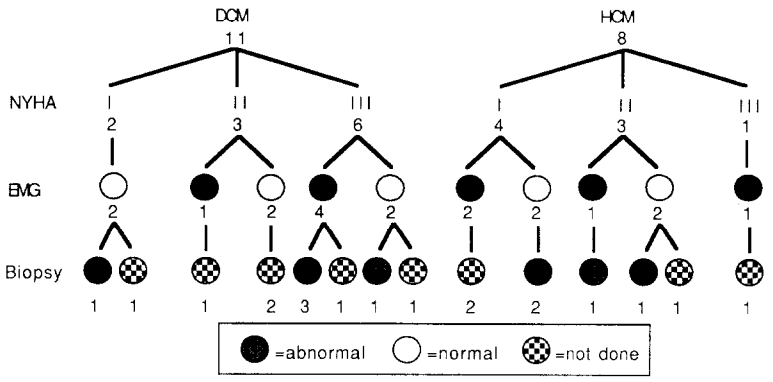

Figure 1. Relation between myogenic abnormalities and New York Heart Association (NYHA) functional class. DCM = dilated cardiomyopathy; EMG = electromyography; HCM = hypertrophic cardiomyopathy.

JACC Vol. 14, No. 6
November 15, 1989:1464–73

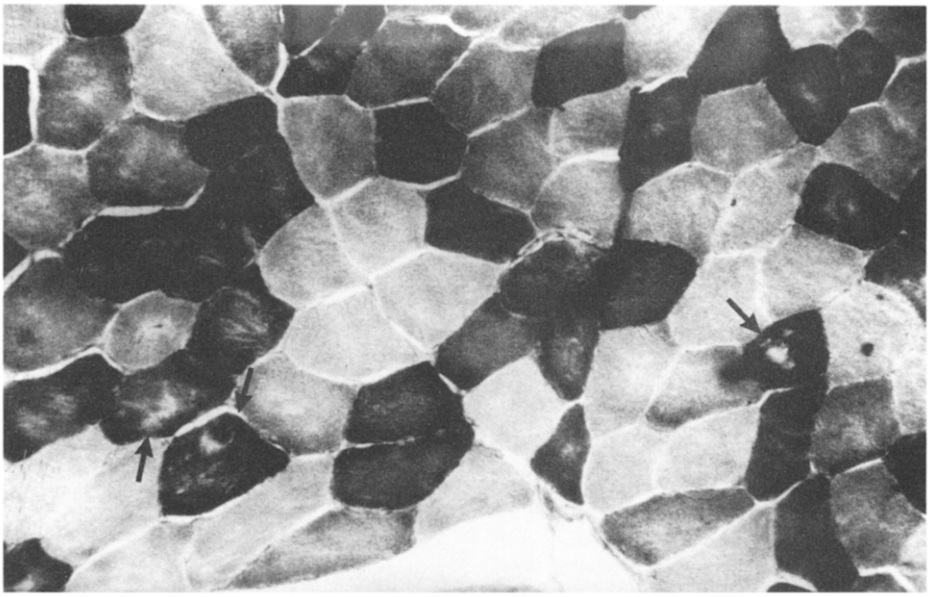

Figure 2. Case 11 (dilated cardiomyopathy. Skeletal biopsy: light microscopy. **Arrows** indicate atrophic type 1 fibers with evident central hyporeactive cores. (Reduced diphosphopyridine nucleotide–tetrazolium reductase stain, original magnification ×200, reduced by 30%.)

sarcolemmal reaction to reduced diphosphopyridine nucleotide-tetrazolium reductase (Fig. 3), or both. Morphometric analysis of type 1 fibers showed increases of atrophy factors in eight of the nine biopsies (mean increase compared with sex-matched normal values were 371%), reduced fiber mean diameter in three patients (two with dilated and one with hypertrophic cardiomyopathy) and type 1 fiber prevalence in one patient with dilated cardiomyopathy (Table 3). No alteration of type 2 fibers was observed in any patient (Table 3).

Of these nine patients, four, whose biopsy specimen was obtained from the biceps brachii muscle, had abnormal results in this muscle at qualitative electromyography and abnormal results in the vastus medialis at quantitative electromyography. The five patients in whom the biopsy was performed in the deltoid (three patients) or in the biceps brachii (two patients), had normal electromyographic results (Fig. 1).

Electron microscopy. Minimal abnormalities of the myofilaments, such as small focal areas with myofibril loss and disruption of the normal banding patterns, were present in two patients with dilated and in three with hypertrophic cardiomyopathy. Lipid vacuoles, scattered along the myofibrils, were detected in three patients with dilated and in

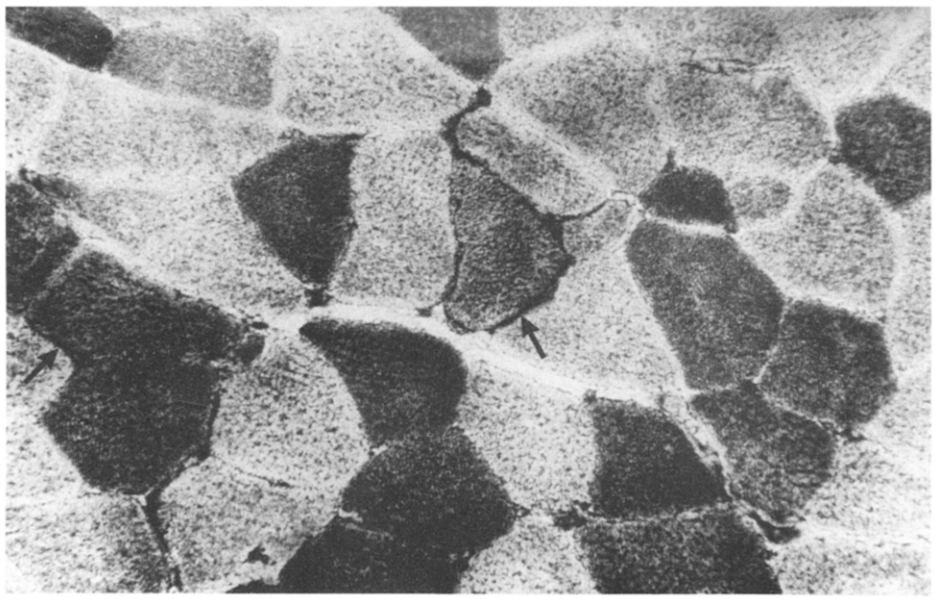

Figure 3. Case 9 (dilated cardiomyopathy). Skeletal biopsy: light microscopy showing strong reaction of subsarcolemmal region in type 1 fibers (**arrows**). (Reduced diphosphopyridine nucleotide–tetrazolium reductase stain, original magnification ×300, reduced by 30%.)

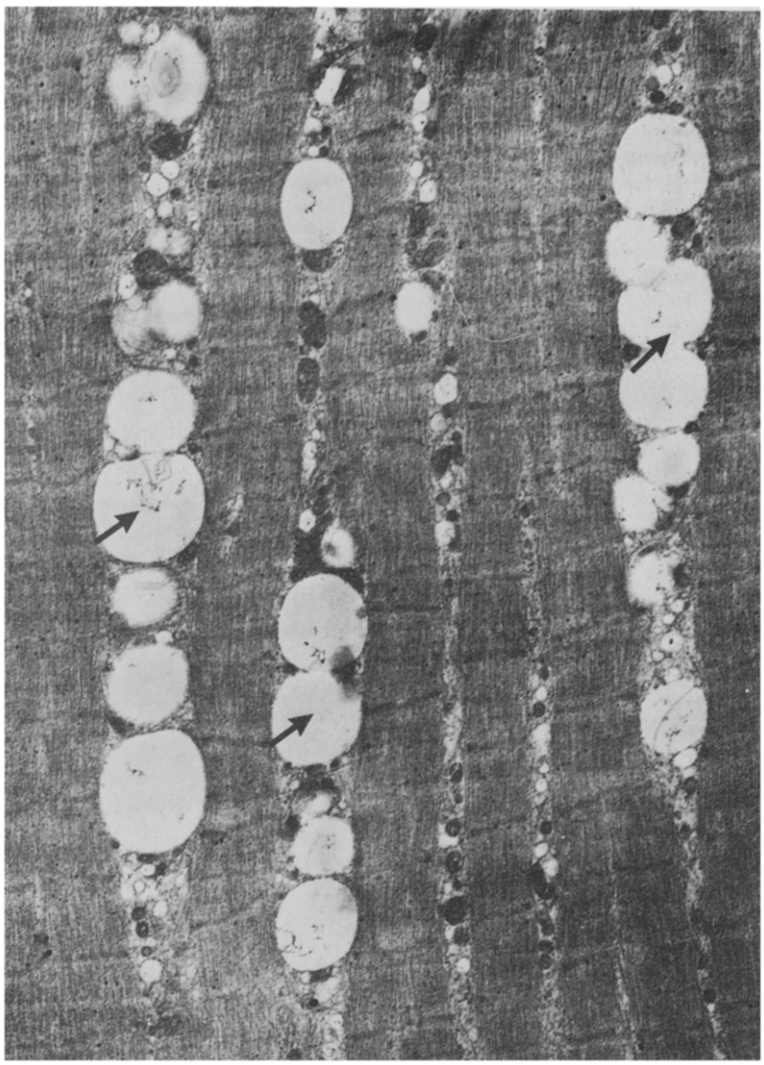

Figure 4. Case 18 (hypertrophic cardiomyopathy). Skeletal biopsy: electron microscopic ultra thin section showing many lipid droplets (**arrows**) among myofibrils (Original magnification ×15,000, reduced by 20%.)

three with hypertrophic cardiomyopathy; in two patients with hypertrophic cardiomyopathy they were particularly large and numerous (Fig. 4). Mitochondrial abnormalities, manifest as swelling with clarification of the matrix, cristolysis and collections of normal or degenerated mitochondria beneath the sarcolemma or in widened spaces between normal or damaged myofibrils, were detected in all patients in both groups (Fig. 5 and 6).

Biochemistry (Table 4). Muscle and serum esterified carnitine levels were abnormally reduced in one patient with hypertrophic cardiomyopathy. Mitochondrial enzymatic activities were reduced for one or more enzymes in one of two patients with dilated and in three of four with hypertrophic cardiomyopathy. Specifically, succinic cytochrome C-reductase was reduced in four patients, reduced diphosphopyridine nucleotide-dehydrogenase and reduced diphosphopyridine nucleotide-cytochrome C-reductase were reduced in 2 and succinic dehydrogenase was reduced in 1 patient. Cytrate synthetase and cytochrome-C-oxidase were normal.

Relation Between Myopathy and Cardiac Function

Echocardiographic and hemodynamic indexes of ventricular function in patients with electromyographic abnormalities were similar to those of patients without (echocardiographic percent fractional shortening 21 ± 9 versus 25 ± 10; angiographic percent ejection fraction 39 ± 13 versus 42 ± 13; left ventricular end-diastolic pressure 21 ± 6 versus 21 ± 8 mm Hg, all p = NS) as was symptom duration (9 ± 4 versus 12 ± 8 months, p = NS).

Electromyographic abnormalities are slightly but not significantly more common in patients in functional class III (5 of 7, 71%) than in those in class I (2 of 6, 33%) or II (2 of 6, 33%) (Fig. 1).

JACC Vol. 14, No. 6
November 15, 1989:1464–73

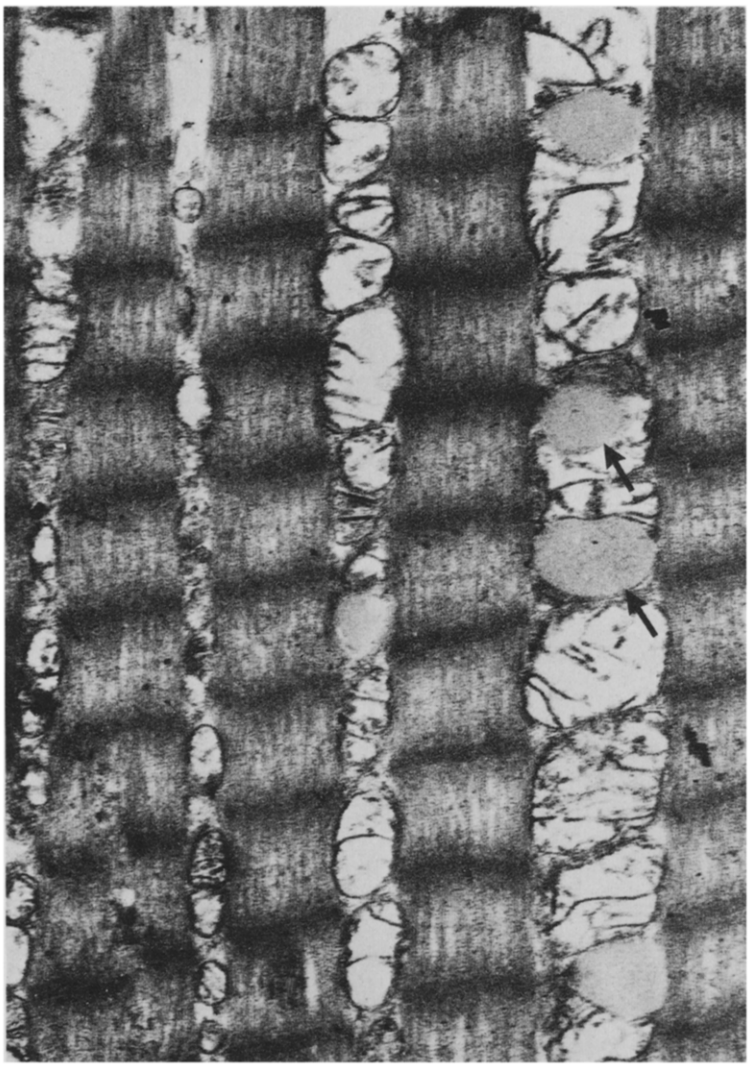

Figure 5. Case 12 (hypertrophic nonobstructive cardiomyopathy). Skeletal biopsy. Electron microscopy shows evidence of severe mitochondrial degenerative changes (swelling, loss of cristae, clarification of the matrix); **arrows** indicate lipid droplets among mitochondria. (Original magnification ×15,000, reduced by 20%.)

Type 1 fiber atrophy factors, indexes of the severity of myopathic changes, were similar in patients in functional class I, II and III (mean increases 371%, 173%, 390%, respectively, p = NS).

Discussion

Electromyographic evidence of myogenic myopathy. Our study provides an objective assessment of skeletal muscle function by quantitative electromyography in patients with dilated and hypertrophic cardiomyopathy. Skeletal muscle abnormalities, in particular reduction of single motor unit potential duration, were found in about 40% of patients with dilated or hypertrophic cardiomyopathy who had no evidence of overt clinical skeletal myopathy. In the absence of traumatic nerve lesions or disorders of neuromuscular transmission, or both, neither of which was present in our patients, these findings are specific for myogenic myopathy (20). In no patient were objective signs of neurogenic alteration, such as reduction of nerve conduction velocities, increase in single motor unit potential duration, Willison ratio or motor unit fiber density, observed (20–24,26). Although this latter variable was determined in the upper limbs only, because chronic edema or lumboarthrosis at a subclinical stage may interfere with its determination in the leg muscles (15,26), peripheral neuropathies may be ruled out because they usually affect distal muscles of both upper and lower limbs and result in reduced nerve conduction velocities (15,20).

Axonal neuropathies, which may primarily affect distal leg muscles with normal nerve conduction velocities (15), were ruled out in our patients. These rare diseases, often severely symptomatic, are either hereditary or toxic (15) and were excluded on clinical grounds.

Our results also show that standard electromyography is less sensitive than quantitative electromyography in detect-

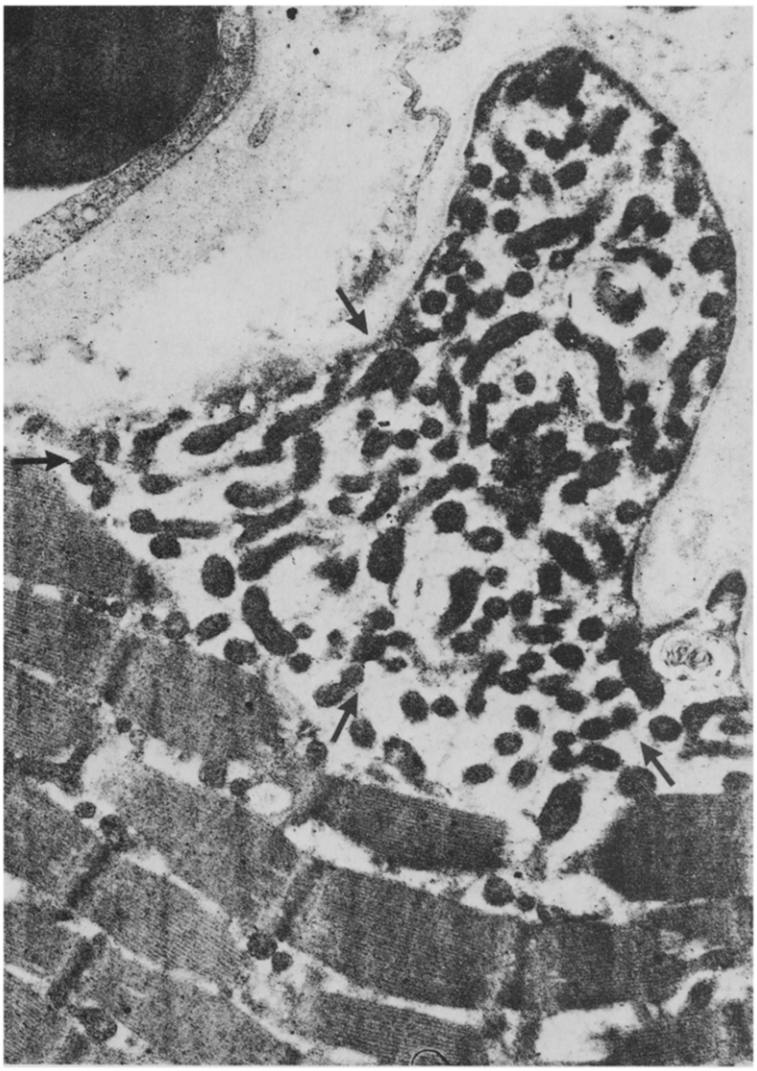

Figure 6. Case 18 (hypertrophic cardiomyopathy). Skeletal biopsy. Electron microscopy of a muscle fiber showing extensive subsarcolemmal accumulation of pyknotic mitochondria (**arrows**). (Original magnification ×20,000, reduced by 20%.)

Table 4. Mitochondrial Enzymatic Activities in Muscle Biopsy (μmol/min/g wet weight) in Six Patients

Patient No.	Citrate Synthetase	Cytochrome-C Oxidase	Reduced Diphosphopyridine Nucleotide Cytochrome-C Reductase	Reduced Diphosphopyridine Nucleotide Dehydrogenase	Succinic Cytochrome-C Reductase	Succinic Dehydrogenase
DCM						
9	14.33 (N)	2.59 (N)	2.70 (N)	33.87 (N)	0.70 (N)	0.62 (N)
11	16.17 (N)	1.21 (N)	1.94 (N)	25.16 (↓)	0.50 (↓)	0.58 (N)
HCM						
12	17.20 (N)	1.84 (N)	1.45 (↓)	45.16 (N)	0.54 (↓)	0.62 (N)
14	12.31 (N)	2.27 (N)	2.70 (N)	35.48 (N)	0.75 (N)	0.58 (N)
16	13.23 (N)	2.10 (N)	2.37 (N)	38.70 (N)	0.51 (↓)	0.62 (N)
18	17.64 (N)	1.37 (N)	1.06 (↓)	26.77 (↓)	0.44 (↓)	0.50 (↓)
Normal (n = 12)	10.14 to 18.38	1.10 to 4.41	1.89 to 7.02	33.64 to 66.12	0.70 to 1.81	0.51 to 2.02

Abbreviations and symbols as in Tables 1 and 2.

JACC Vol. 14, No. 6
November 15, 1989:1464–73

ing myopathies. This could explain why other investigators did not find skeletal muscle abnormalities in patients with dilated or hypertrophic cardiomyopathy (8,9).

Histologic evidence of myogenic myopathy. In this study skeletal muscle biopsy always confirmed the presence of myogenic myopathy as indicated by selective type 1 fiber alterations. Electromyographic and histopathologic abnormalities were similar in patients with dilated and those with hypertrophic cardiomyopathy. These findings are intriguing and no clear explanation is available. The selective type 1 fiber atrophy described in this study, similar to that described in congenital and idiopathic myopathies (1,29–39), has not been previously reported in patients with dilated and hypertrophic cardiomyopathy. Others (3,4) reported type 2 fiber atrophy in patients with dilated cardiomyopathy. However, type 2 fiber atrophy is not specific for myogenic myopathy; it is also seen in neurogenic atrophy (30), disuse atrophy (29) and, in particular, in peripheral vascular disease (40,41) and cardiac failure (1,42). The selective involvement of type 1 fibers, which have predominant oxidative metabolism, and the reduced activity of mitochondrial oxidative enzymes are in agreement with findings of recent studies using nuclear magnetic resonance spectral analysis, which show impaired oxidative metabolism in skeletal muscle of patients with cardiomyopathy whether or not heart failure is present (43,44).

Histologic myogenic changes were detected even in the absence of functional abnormalities in five patients, suggesting that such changes are an earlier marker of myogenic myopathy. Sequential biopsies and electromyographic studies might better delineate the natural history of the myopathic involvement in patients with cardiomyopathy. However, the invasive nature of the procedure represents an objective limitation of this approach.

The mechanism of myogenic myopathy in our patients is unknown. In one patient, who had severe ultrastructural mitochondrial changes and reduced concentrations of carnitine fractions both in serum and in muscle, a defect in carnitine esterification was postulated as a mechanism (32–35).

Relation between skeletal myopathy and heart failure. The design of the present study does not allow us to establish whether myopathic changes are primary or secondary to heart failure. However, the following observations argue against the latter possibility: 1) selective type 1 atrophy is typically observed in congenital or idiopathic myopathies (29–32) but not in secondary heart failure (1,42); 2) the severity of myogenic myopathy, as assessed by type 1 fiber atrophy factors, was similar among patients in cardiac functional classes I, II and III; 3) echocardiographic and hemodynamic indexes of left ventricular function were similar in patients with and without electromyographic abnormalities; and 4) the proportions of patients with electromyographic abnormalities were not statistically different in the three functional classes.

We gratefully acknowledge William J. McKenna, MD, for thoughtful advice and constructive criticism, Jan Poloniecki for statistical analysis and Shaughan Dickie for technical assistance in preparing the manuscript.

References

1. Shafiq SA, Sande MA, Carruthers RR, Killip T, Milborat AT. Skeletal muscle in idiopathic cardiomyopathy. J Neurol Sci 1972;15:303–20.
2. Isaacs H, Muncke G. Idiopathic cardiomyopathy and skeletal muscle abnormality. Am Heart J 1975;90:767–73.
3. Dunnigan A, Pierpont ME, Smith SA, Breningstall G, Benditt DG, Benson DW. Cardiac and skeletal myopathy associated with cardiac dysrhythmias. Am J Cardiol 1984;53:731–7.
4. Dunnigan A, Staley NA, Smith SA, et al. Cardiac and skeletal muscle abnormalities in cardiomyopathy: comparison of patients with ventricular tachycardia or congestive heart failure. J Am Coll Cardiol 1987;10:608–18.
5. Smith ER, Heffernan LP, Sangalang VE, Vaughan LM, Flamington CS. Voluntary muscle involvement in hypertrophic cardiomyopathy: a study of 11 patients. Ann Intern Med 1976;85:566–72.
6. Hootsmans WJM, Meerschwam IS. Electromyography in patients with hypertrophic obstructive cardiomyopathy. Neurology 1971;21:810–16.
7. Meerschwam IS, Hootsmans WJM. An electromyographic study in hypertrophic obstructive cardiomyopathy. In: Wolsterholme GEW, O'Connor M, London J, Churchill A, eds. Hypertrophic Obstructive Cardiomyopathy. Ciba Foundation Study Group No. 37. New York: Wiley. 1971:55–62.
8. Przybosewki JZ, Hoffman HD, Graff AS, et al. A study of a family with inherited disease of cardiac and skeletal muscle. Part 1: Clinical electrocardiographic, echocardiographic, hemodynamic, electrophysiological and electron microscopic studies. S Afr Med J 1981;59:363–73.
9. Lochner A, Hewlett RH, O'Kennedy A, et al. A study of a family with inherited disease of cardiac and skeletal muscle. Part 2: skeletal muscle morphology and mitochondrial oxidative phosphorilation. S Afr Med J 1981;59:453–61.
10. Thorn GW, Cahill GF Jr. Gain in weight: obesity. In: Wintrobe MM, Thorn GW, Adams RD, Braunwald E, Isselbacher KJ, Petersdorf RG, eds. Harrison's Principles of Internal Medicine. New York: McGraw-Hill, 1974:232–6.
11. Brandenburg RO, Chazov E, Cherian G, et al. Report of WHO/ISFC Task Force on Definition and Classification of the Cardiomyopathies. Circulation 1981;64:437–8A.
12. Goodwin JF, Oakley CM. The cardiomyopathies. Br Heart J 1972; 34:345–52.
13. Maron BJ, Gottdiener JS, Epstein SE. Pattern and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a wide angle two-dimensional echocardiographic study of 125 patients. Am J Cardiol 1981;48:418–28.
14. Shapiro LM, McKenna WJ. Distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: a two-dimensional echocardiographic study. J Am Coll Cardiol 1983;2:437–44.
15. Dyck PJ, Thomas PK, Lambert EH. Peripheral Neuropathy. Philadelphia: WB Saunders, 1975:321–5.
16. Brooke MH, Griggs RC, Mendell JR, Finichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy. I. The design of the protocol. Muscle Nerve 1981;4:186–97.
17. Scott OM, Goddard C, Dubowitz V. Quantitation of muscle function in children: a prospective study in Duchenne muscular dystrophy. Muscle Nerve 1982;5:291–301.

18. Serratrice G, Gastaut JL, Pellissier JF, Pouget J, Desnuelle C, Cros D. Abrège des maladies musculaires. Paris: Masson, 1982:36.

19. Angelini C, Bresolin N, Pegolo G, et al. Childhood encephalomyopathy with cytochrome C oxidase deficiency, ataxia, muscle wasting and mental impairment. Neurology 1986;36:1048–52.

20. Kimura J. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. Philadelphia: FA Davis, 1984:235, 259.

21. Ref. 20: 259.

22. Willison RG. Analysis of electrical activity in healthy and dystrophic muscles in man. J Neurol Neurosurg Psychiatry 1964;27:386–94.

23. Rose AL, Willison RG. Quantitative electromyography using automatic analysis: study in healthy subjects and patients with primary muscle disease. J Neurol Neurosurg Psychiatry 1967;30:403–10.

24. Stalberg E, Chu J, Bril V, Nandedkar S, Stalberg S, Ericsson M. Automatic analysis of the EMG interference pattern. EEG Clin Neurophys 1983;56:672–81.

25. Troni W, Cantello R, Rainero I. Conduction velocity along human muscle fibers in situ. Neurology 1983;33:1453–9.

26. Stalberg E, Thiele B. Motor unit fiber density in the extensor digitorum communis muscle. Single fiber electromyographic study in normal subjects at different ages. J Neurol Neurosurg Psychiatry 1975;38:874–80.

27. Ref 20: 247.

28. Dubowitz V, Brooke MH. Definition of pathological changes seen in muscle biopsies. In: Dubowitz V, Brooke MH, eds. Muscle Biopsy: A Modern Approach. Philadelphia: WB Saunders, 1973:74–102.

29. Dubowitz V. Histochemical aspects of muscle disease. In: Walton J, ed. Disorders of Voluntary Muscle. New York: Churchill Livingstone, 1981: 261–95.

30. Engel WK. Selective and non selective susceptibility of muscle fiber types. Arch Neurol 1970;22:97–117.

31. Mastaglia FL, Hudgson P. Ultratructural studies of diseased muscle. In: Walton J, ed. Disorders of Voluntary Muscle. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1981:297–356.

32. Di Mauro S, Trevisan C, Hays A. Disorders of lipid metabolism in muscle. Muscle Nerve 1980;3:369–88.

33. Boudin G, Mikol J, Guillard A, Engel AG. Fatal systemic carnitine deficiency with lipid storage in skeletal muscle, heart, liver and kidney. J Neurol Sci 1976;30:313–25.

34. Hart ZH, Chang CH, Di Mauro S, Farroki Q, Ayyar R. Muscle carnitine deficiency and fatal cardiomyopathy. Neurology 1978;28:147–51.

35. Waber LJ, Valle D, Neill C, Di Mauro S, Shug A. Carnitine deficiency presenting as familial cardiomyopathy: a treatable defect in carnitine transport. J Pediatr 1982;101:700–5.

36. Stoessl AJ, Hahn AF, Malot D, Jones DT, Silver MD. Nemaline myopathy with associated cardiomyopathy. Report of clinical and detailed autopsy findings. Arch Neurol 1985;42:1084–6.

37. Meier C, Gertsch M, Zimmermann A, Voellmy W, Geissbuhler J. Nemaline myopathy presenting as cardiomyopathy. N Engl J Med 1983; 308:1536–7.

38. Meier C, Voellmy W, Gertsch M, Zimmermann A, Geissbuhler J. Nemaline myopathy appearing in adults as cardiomyopathy: a clinicopathological study. Arch Neurol 1984;41:443–5.

39. Hübner G, Grantzow R. Mitochondrial cardiomyopathy with involvement of skeletal muscles. Virchows Arch (Pathol Anat) 1983;399:115–25.

40. Clyne CAC, Mears H, Weller RO, O'Donnell TF. Calf muscle adaptation to peripheral vascular disease. Cardiovasc Res 1985;19:507–12.

41. Henriksson J, Nygaard E, Anderson J, Eklof B. Enzyme activities, fiber types and capillarization in calf muscles of patients with intermittent claudication. Scand J Clin Lab Invest 1980;40:361–9.

42. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA. Abnormalities of skeletal muscle in patients with chronic heart failure. Int J Cardiol 1988;18:187–95.

43. Massie BM, Conway M, Yonge R, et al. ^{31}P nuclear magnetic resonance evidence for abnormal skeletal muscle metabolism in patients with congestive heart failure. Am J Cardiol 1987;60:309–15.

44. Rajagopalan B, McKenna WJ, Yonge RYY, Radda GK. Evidence of impaired oxidative metabolism in skeletal muscle in hypertrophic cardiomyopathy: a ^{31}P magnetic resonance spectroscopy study (Abstr) Circulation 1987;76(suppl IV):IV-250.